33. The pharmaceutical composition of claim 21, wherein said composition is a liquid.

34. The pharmaceutical composition of claim 21, wherein said composition is lyophilized.--

REMARKS

Claims 15-20 have been cancelled without prejudice or disclaimer subject to the Restriction Requirement. Applicants expressly reserve the right to file divisional applications or take such other appropriate measures deemed necessary to protect the inventions in the canceled claims. Claims 1, 3, 4, 5, 11, and 12 have been amended as noted below. New claims 21-34 have been added. Support for the amendments and new claims can be found in the claims as originally filed and in the specification. Accordingly, no new matter has been added.

Specifically, amended claim 1 is directed to a pharmaceutical composition comprising at least one pharmaceutically active agent and a buffer consisting substantially of succinate at a concentration of about 10 mM to about 40 mM and a counterion. Dependent claims 3, 4, 5, and 12 as amended recite specific embodiments of this claim. Support for recitation of succinate concentrations in this range resides in the specification, for example at page 7, lines 17-27. Amended claim 11 clarifies that the pharmaceutically active agent is human IGF-I or variant thereof, where the variant is a polypeptide having IGF-I activity and at least 70% sequence identity to human IGF-I. Support for recitation of these functional and structural features of IGF-I variants is found in the specification, for example, at page 9, lines 20-27, at page 13, lines 7-16, and at page 10; line 27, through page 11, line10. New claims 21-34 are directed to specific embodiments of claim 1.

Claims 1-14 and 21-34 are now pending in the application. Reexamination and reconsideration of the pending claims are respectfully requested. The Examiner's comments in the Office Action are addressed in the order set forth therein.

The Rejections of the Claims under 35 U.S.C. §112, First and Second Paragraphs, Should Be Withdrawn

Claims 1-14 are rejected under 35 U.S.C. §112, first paragraph. The Office Action states that the specification does not enable pharmaceutically active agents or biologically active variants of IGF-1. This rejection is respectfully traversed.

In accordance with the enablement requirement, the specification must adequately disclose to one of skill in the relevant art how to make the claimed invention without undue experimentation. *Process Control Corp. v. Hydreclaim Corp.*, 190 F.3d 1350, 52 USPQ2d 1029 (Fed. Cir. 1999). Applicants note that the Examiner has not explained this rejection or offered any factual evidence in support thereof. For this reason alone, the rejection should be withdrawn.

Nonetheless, Applicants note that the phrase "a pharmaceutically active agent" is defined in the specification as "any pharmaceutically effective compound that is compatible with succinate buffer" (page 8, paragraph 1). At the same paragraph, a list of suitable agents is provided. Further, Applicants note that the invention as broadly claimed does not reside in the particular pharmaceutically active agent within the pharmaceutical formulation. Applicants have discovered that pharmaceutical formulations buffered with succinate cause less pain on injection than other commonly used buffers. Having taught the use of succinate, one of skill in the art can make a pharmaceutical composition using any active agent in combination with succinate. Thus, the phrase "pharmaceutically active agent" read in light of the specification encompasses any agent that is to be injected for purposes of treatment, diagnosis, or prevention. The fact that Applicants have exemplified their invention using IGF-I as the active agent is no reason to limit the claims to IGF-I-containing compositions. As taught throughout the specification, any pharmaceutically active agent may readily be used in the compositions of the invention.

With respect to biologically active variants of IGF-1, this term is defined in the specification as "IGF-I fragments, analogues, and derivatives" (page 8, paragraph 4, lines 2-3). Such variants are known in the art and specifically set forth in the specification. See, for example, page 9, paragraph 2, lines 7-8, and pages 10-13. Furthermore, the claims as amended clearly set forth the functional and structural features characteristic of the claimed variants.

Applicants submit that one of skill in the relevant art would not require undue experimentation to practice the invention as claimed with a particular IGF-1 variant. For all these reasons, the rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Claims 1-14 are rejected under 35 U.S.C. §112, second paragraph, as indefinite. This rejection is respectfully traversed.

The legal standard of definiteness is whether a claim reasonably apprises those of skill in the art of its scope. *See In re Warmerdam*, 33 F.3d 1354, 31 USPQ2d 1754 (Fed. Cir. 1994). Furthermore, the claim must be read in light of the specification. *See, e.g., Credle v. Bond*, 25 F.3d 1566, 30 USPQ2d 1911 (Fed. Cir. 1994).

Claims 1-10, 13, and 14 are rejected based on the terminology "pharmaceutically active agents." The Examiner states that these claims "encompass organic and inorganic agents" and that it is "not clear as to which organic or inorganic agents are intended to claim in the claims." As noted above, Applicants' specification states that pharmaceutically active agents include "any pharmaceutically effective compound that is compatible with succinate buffer" (page 8, paragraph 1). The specification provides as examples of pharmaceutically active agents "organic drugs, inorganic drugs, antibiotics, proteins, peptides, carbohydrates, lipids, fatty acids, nucleic acids and derivatives thereof." Thus the term does encompass any organic and inorganic agents that would be contemplated for use as a pharmaceutically active agent. Applicants respectfully submit that one of skill in the art would recognize that the phrase "pharmaceutically active agent" as used in accordance with the present invention is a definite term that refers to any injectable substance useful for treatment, diagnosis, or prevention. Accordingly, one of skill in the art would be reasonably apprised of the scope of the invention as claimed. In view of these remarks, Applicants respectfully submit that this rejection should be withdrawn.

Claim 9 and dependent claim 10 are rejected as indefinite because of the use of the term "such that" in claim 9. The claim in full recites "the composition of claim 1, further comprising a sufficient concentration of at least one tonicifying agent such that the composition is isotonic." The specification explains how to adjust a solution using a tonicifying agent "such that" it is

isotonic (page 16, paragraph 1, to page 17, especially page 16, paragraph 1). Furthermore, "isotonic" is defined on page 16 of the specification. Examples of tonicifying agents are given, as well as references to methods known in the art for making a solution isotonic. Applicants submit that the term "such that" would be understood by one of skill in the art and, to the extent that it has any impact on the scope of the claim, the term would reasonably apprise one of skill in the art of that scope. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Claims 11 and 12 are rejected as indefinite based on the recitation of the term "a biologically active variant thereof." Amended claims 11 and 12 dependent thereon recite pharmaceutical compositions that comprise human IGF-I or biologically active variant thereof, where the variant is a polypeptide having IGF-I activity and at least 70% sequence identity to human IGF-I. Applicants submit that the phrase "insulin-like growth factor 1 or a biologically active variant thereof" is defined in the specification (page 8, paragraph 4, lines 2-3). Further, variants of human IGF-1 are known in the art (specification, page 9, paragraph 2, lines 7-8, and pages 10-13). Applicants submit that the term "a biologically active variant thereof" would reasonably apprise one of skill in the art of the scope of claims 11 and 12. Applicants respectfully request that this rejection be withdrawn.

The Rejections of the Claims under 35 U.S.C. §102(b) Should Be Withdrawn

Claims 1-3, 6-9, 11, and 12 are rejected under 35 U.S.C. §102(b). These rejections are respectfully traversed.

The Examiner rejects claims 1-3 and 6-9 over EPA 0 284 249 (the '249 application), which discloses interferon in a 50 mM succinate buffer with a counterion. Amended claim 1 recites a pharmaceutical composition comprising at least one pharmaceutically active agent and "a buffer, wherein said buffer consists substantially of succinate at a concentration of about 10 mM to about 40 mM and a counterion." The '249 application does not teach such a composition, and thus it does not anticipate claim 1 or claims 2, 3, or 6-9 dependent thereon. In view of this, Applicants respectfully submit that this rejection should be withdrawn.

Claims 11 and 12 are rejected as being anticipated by Clark *et al.*, U.S. Patent No. 5,374,620 (the '620 patent), which teaches IGF-1 and growth hormone in an acetic acid buffer. Claims 11 and 12 depend from amended claim 1, which, as noted above, recites "a buffer, wherein said buffer consists substantially of succinate at a concentration of about 10 mM to about 40 mM and a counterion." The '620 patent does not recite any concentration limitation for a succinate buffer, however, and only mentions succinate briefly in the following passage:

> Examples include acetic acid salt buffer, which is any salt of acetic acid, including sodium acetate and potassium acetate, succinate buffer, phosphate buffer, citrate buffer, or any others known to the art to have the desired effect. The most preferred buffer is sodium acetate, optionally in combination with sodium citrate.

('620 patent, column 8-14). The '620 patent does not teach all of the limitations of these claims, and thus, it does not anticipate claims 11 and 12. In view of this, Applicants respectfully request that the rejection be withdrawn.

The Rejection of the Claims under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 1-14 are rejected under 35 U.S.C. §103(a) over the '620 patent in light of the '249 patent. This rejection is respectfully traversed.

To establish a *prima facie* case of obviousness (1) there must be some suggestion in the reference or knowledge generally available to one of ordinary skill in the art to modify the reference or combine the references; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations. MPEP § 2143. Here, the references cited by the Examiner, alone or in combination, do not teach or suggest the molarity limitation of these amended claims. For this reason alone, the Examiner's rejection is obviated. Further, the '620 patent teaches away from the use of succinate buffer, stating that the preferred buffer is sodium acetate (above).

Claims 1-14 are directed to pharmaceutical compositions comprising at least one pharmaceutically active agent and a buffer that consists substantially of succinate at a concentration of about 10 mM to about 40 mM and a counterion. As noted elsewhere

herein, Applicants have discovered that pharmaceutical formulations that are buffered with succinate at concentration ranges disclosed in the application have reduced pain upon injection relative to those formulated with other buffers at similar concentrations. Applicants respectfully submit that the cited references do not teach or suggest Applicants' claimed invention. As such, this rejection should be withdrawn.

New Claims Presented

New claims 21 to 34 are directed to pharmaceutical compositions comprising human IGF-I and succinate buffer as noted therein. The compositions are specific embodiments of claim 1. Support for these claims resides throughout the specification and in the claims as originally filed. See, for example, pages 7 and 8. The cited references do not anticipate or render obvious these new claims.

CONCLUSION

In view of the aforementioned amendments and remarks, Applicants respectfully submit that the rejections of the claims under 35 U.S. C. §112, first and second paragraph, §102(b), and 103(a) are overcome and that this application is now in condition for allowance. Early notice to this effect is solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required

therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

Leslie T. Henry
Registration No. 45,714

Customer No. 000826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 420-2200
Fax Raleigh Office (919) 420-2260

CERTIFICATION OF FACSIMILE TRANSMISSION	CERTIFICATE OF MAILING
I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office at Fax No. on the date shown below. _____ (Type or print name of person signing certification.) _____ Signature Date	I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on June 28, 2001. Polly P. Burton Polly P. Burton

Version with Markings to Show Changes Made:

Please amend claims 1, 3, 4, 5, 11, and 12 as follows:

1. (Amended) A pharmaceutical composition comprising at least one pharmaceutically active agent and a buffer, wherein said buffer consists substantially of succinate at a concentration of about 10 mM to about 40 mM and a counterion.

3. (Amended) The composition of claim 1, wherein the concentration of succinate is about [0.5-100]10 mM to about 30 mM.

4. The composition of claim 3, wherein the concentration [range for said]of succinate [compound] is about [2-20]10 mM to about 20 mM.

5. The composition of claim 4, wherein the concentration of [said] succinate [compound] is about 10 mM.

11. (Amended) The composition of claim 1, wherein said pharmaceutically active compound is human insulin-like growth factor 1 (IGF-I) or a biologically active variant thereof, wherein said variant is a polypeptide having IGF-I activity and at least 70% sequence identity to human IGF-I.

12. The pharmaceutical composition of claim 11, wherein the pH of said composition is about 6.0, the concentration of said succinate [compound] is about 10 mM, and the composition further comprises about 140 mM sodium chloride.